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EDITORIAL COMMENT

Lessons From the Heart

Troponin Elevations in Patients With Established Peripheral Artery Disease*

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The prevalence of peripheral artery disease (PAD) is estimated to be approximately 4.3% among U.S. adults older than 40 years of age and close to 15% in those 75 years and older (1). Patients with established PAD have a high probability of atherosclerosis in other vascular beds (2) and are at increased risk for myocardial infarction, stroke, and death, as well as limb ischemic events that lead to peripheral revascularization procedures and amputations (3). Data from the international REACH (REduction of Atherothrombosis for Continued Health) registry indicate that the annual risk of cardiovascular death, myocardial infarction, and stroke in patients with PAD can range from 4% to 5% for patients with intermittent claudication to 8% for those with ischemic amputations (3,4).

See page 1529

Interestingly, despite the increased risk and variability of outcomes in patients with PAD, risk stratification has received relatively little attention in this population. This contrasts sharply with patients who have established coronary artery disease (CAD), where extensive investigation has been performed to identify tools to enhance risk assessment. Factors that have been associated with worse outcomes in PAD patients include older age, smoking, diabetes, and polyvascular disease (4). The most widely studied biomarker for risk assessment in patients with PAD is high-sensitivity C-reactive protein (hs-CRP). Previous studies have investigated hs-CRP in generally lower-risk PAD cohorts and have reported increased cardiac event rates in patients with higher hs-CRP levels, independent of measurements of disease severity such as the ankle/brachial index (5,6). However, the strength of association between hs-CRP and ischemia-related and fatal outcomes has been modest. Moreover, as this population already has an indication for statin therapy and as hs-CRP correlates poorly with the extent of CAD (7), there are no clear clinical implications related to higher levels of this inflammatory biomarker. Additionally, the utility of CRP in higher acuity patients in the hospitalized setting is not clear. Several studies have also assessed the prognostic utility of N-terminal pro–B-type natriuretic peptide in patients with PAD (8,9), with inconsistent results reported among studies.

Recently, there has been an interest in exploring the role of pre-procedural measurements of cardiac troponin T (cTnT) concentrations for risk stratification in PAD patients referred for surgical or endovascular revascularization procedures. Although previous studies have clearly linked post-operative troponin elevations with increased risk of myocardial infarction and both short- and long-term mortality (10), much less is known about troponin measurements performed before the revascularization procedure. Following publication of several favorable pilot studies (11,12), Linnemann et al. (13) recently reported findings for 254 patients presenting with acute limb ischemia and undergoing endovascular intervention at their institution in 2007 and noted that a cTnT concentration above the detection range (≥0.01 ng/ml) at admission was independently associated with in-hospital mortality and amputations. In this issue of the *Journal*, these authors extend their findings to 1,065 patients with symptomatic PAD undergoing an endovascular intervention at a single institution (14). cTnT was detectable (≥0.01 ng/ml) in more than 21% of all patients. Predictably, these patients were older and had a larger burden of comorbidities. One-year mortality rates in patients with detectable cTnT levels were >8-fold higher than in those with undetectable pre-operative cTnT levels, even after adjusting for potential confounders in multivariable analyses. However, amputations were not different in adjusted analyses between patients with and those without cTnT elevation (14).

Because cTnT was measured only at admission in the present study, it was not possible to determine whether cTnT elevations were acute or chronic. In addition, the cause of cTnT elevation is unclear. Although patients with acute cardiac and noncardiac conditions that commonly lead to troponin elevation (acute coronary syndromes, pulmonary embolism, acute heart failure) were excluded from the current study, troponin levels are frequently acutely elevated among patients hospitalized with significant medical or surgical illnesses, even when one of the aforementioned conditions is not present. Troponin elevation in such patients may be caused by silent myocardial infarction (MI) caused by plaque rupture (type 1 MI), by supply–demand mismatch (type 2 MI), and by direct and indirect cardiac injury from nonischemic mechanisms (15). In addition, it is increasingly recognized that *chronic* troponin elevations are commonly seen among patients with chronic coronary

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disease, heart failure, or kidney disease, as well as those with asymptomatic left ventricular hypertrophy and left ventricular dysfunction (16,17). The troponin elevations detected at the time of admission in the present study likely represented an admixture of several of these acute and chronic conditions.

Several additional caveats to the present study merit comment. First, the investigators used a standard cTnT assay rather than a high-sensitivity troponin assay. With the high-sensitivity cTnT assay, >90% of individuals with chronic CAD or heart failure have measurable cTnT levels (18,19). Studies in patients with chronic cardiovascular disease show graded associations between troponin levels, and death and heart failure outcomes, even at levels of cTnT well below the detection range of standard assays (18,19). One would expect an even higher proportion of PAD patients would have detectable troponin levels with high-sensitivity assays. The quantitative information provided by the high-sensitivity troponin assays may allow more refined risk stratification than is possible with the standard cTnT assay used by Linnemann et al. (14) in the current study. Second, the investigators do not report other important cardiovascular outcomes such as heart failure. In previous studies, even among patients with CAD, small elevations in cTnT concentrations associated more robustly with heart failure events than with ischemic events (19). Information about heart failure would have been helpful because it might have helped to explain the extremely high mortality rate in the cTnT-positive patients (>30% at 1 year), despite only a 4.1% incidence of MI.

How might the information reported by Linnemann et al. (14) be of potential value for clinicians caring for PAD patients undergoing endovascular procedures? PAD is already considered a Class I indication for antiplatelet and statin therapy (20), recommendations that are unlikely to change based on troponin values. Unfortunately, the utilization of evidence-based secondary prevention measures in these patients remains suboptimal (21), and measures to enhance adherence are urgently needed. In the current study, although most patients were on aspirin at discharge, nearly 30% were discharged without a statin. Systems-based approaches to improve adherence with this measure at discharge, as have been instituted for patients with acute myocardial infarction, may be helpful (22).

Although myocardial infarction rates were increased among patients with cTnT elevation in the current study, randomized controlled trials have not demonstrated a benefit from coronary revascularization before surgical peripheral arterial revascularization (23), or from pre-operative initiation of beta-blocker therapy (24). It remains possible that enhanced risk assessment using troponin measurements or other risk stratification tools may help to identify extremely high-risk subgroups that derive benefit from periprocedural beta-blockers or coronary revascularization, but this hypothesis must be tested in adequately powered clinical trials.

Given the very high risk observed in patients with limb ischemia when troponin elevation is detected, consideration should be given to strategies that may prevent elevated troponin levels in the first place. Of course, this assumes a causal relationship of troponin elevation and adverse outcomes in this patient population, a hypothesis that remains to be proven. Data from community-based cohorts have reported associations of baseline HbA_{1c} measurements and fitness levels with subsequent troponin elevation (25,26). These observations suggest the possibility that enhanced glycemic control and exercise may modify the cardiac injury process and could prevent some of the troponin elevations seen in this population.

The investigators are to be congratulated for performing one of the largest risk stratification studies in patients with symptomatic PAD. Whereas previous studies have used small and highly selected cohorts, the present study is large and representative of the high-acuity patients frequently seen by vascular medicine specialists. We hope these data will help set the stage for future large and more comprehensive studies to improve risk stratification in this complex and understudied population.

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REFERENCES

1. Selvin E, Erlinger TP. Prevalence of and risk factors for peripheral arterial disease in the United States: results from the National Health and Nutrition Examination Survey, 1999–2000. Circulation 2004;110:738–43.
2. Bhatt DL, Steg PG, Ohman EM, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. JAMA 2006;295:180–9.
3. Steg PG, Bhatt DL, Wilson PW, et al. One-year cardiovascular event rates in outpatients with atherothrombosis. JAMA 2007;297:1197–206.
4. Bhatt DL, Eagle KA, Ohman EM, et al. Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. JAMA 2010;304:1350–7.
5. Criqui MH, Ho LA, Denenberg JO, Ridker PM, Wassel CL, McDermott MM. Biomarkers in peripheral arterial disease patients and near- and longer-term mortality. J Vasc Surg 2010;52:85–90.
6. Vidula H, Tian L, Liu K, et al. Biomarkers of inflammation and thrombosis as predictors of near-term mortality in patients with peripheral arterial disease: a cohort study. Ann Intern Med 2008;148:85–93.
7. Khera A, de Lemos JA, Peshock RM, et al. Relationship between C-reactive protein and subclinical atherosclerosis: the Dallas Heart Study. Circulation 2006;113:38–43.
8. Mueller T, Dieplinger B, Poelz W, Endler G, Wagner OF, Haltmayer M. Amino-terminal pro-B-type natriuretic peptide as predictor of mortality in patients with symptomatic peripheral arterial disease: 5-year follow-up data from the Linz Peripheral Arterial Disease Study. Clin Chem 2009;55:68–77.
9. Shadman R, Allison MA, Criqui MH. Glomerular filtration rate and N-terminal pro-brain natriuretic peptide as predictors of cardiovascular mortality in vascular patients. J Am Coll Cardiol 2007;49:2172–81.
10. Kim LJ, Martinez EA, Faraday N, et al. Cardiac troponin I predicts short-term mortality in vascular surgery patients. Circulation 2002;106:2366–71.

11. Rittoo D, Stahnke M, Lindesay C, Grocott E, Hickey N, Downing R. Prognostic significance of raised cardiac troponin T in patients presenting with acute limb ischaemia. Eur J Vasc Endovasc Surg 2006;32:500–3.
12. Sarveswaran J, Ikponmwosa A, Asthana S, Spark JI. Should cardiac troponins be used as a risk stratification tool for patients with chronic critical limb ischaemia? Eur J Vasc Endovasc Surg 2007;33:703–7.
13. Linnemann B, Sutter T, Sixt S, et al. Elevated cardiac troponin T contributes to prediction of worse in-hospital outcomes after endovascular therapy for acute limb ischemia. J Vasc Surg 2012;55:721–9.
14. Linnemann B, Sutter T, Hermman E, et al. Elevated cardiac troponin T is associated with higher mortality and amputation rates in patients with peripheral arterial disease. J Am Coll Cardiol 2014;63:1529–38.
15. Newby LK, Jesse RL, Babb JD, et al. ACCF 2012 expert consensus document on practical clinical considerations in the interpretation of troponin elevations: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol 2012;60:2427–63.
16. Eggers KM, Lagerqvist B, Venge P, Wallentin L, Lindahl B. Persistent cardiac troponin I elevation in stabilized patients after an episode of acute coronary syndrome predicts long-term mortality. Circulation 2007;116:1907–14.
17. Wallace TW, Abdullah SM, Drazner MH, et al. Prevalence and determinants of troponin T elevation in the general population. Circulation 2006;113:1958–65.
18. Latini R, Masson S, Anand IS, et al. Prognostic value of very low plasma concentrations of troponin T in patients with stable chronic heart failure. Circulation 2007;116:1242–9.
19. Omland T, de Lemos JA, Sabatine MS, et al. A sensitive cardiac troponin T assay in stable coronary artery disease. N Engl J Med 2009;361:2538–47.
20. Rooke TW, Hirsch AT, Misra S, et al. 2011 ACCF/AHA focused update of the guideline for the management of patients with peripheral artery disease (updating the 2005 guideline): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2011;58:2020–45.
21. Kumbhani DJ, Steg PG, Cannon CP, et al. Adherence to secondary prevention medications and four-year outcomes in outpatients with atherosclerosis. Am J Med 2013;126:693–700.e1.
22. Kumbhani DJ, Fonarow GC, Cannon CP, et al. Predictors of adherence to performance measures in patients with acute myocardial infarction. Am J Med 2013;126:74.e1–9.
23. McFalls EO, Ward HB, Moritz TE, et al. Coronary-artery revascularization before elective major vascular surgery. N Engl J Med 2004;351:2795–804.
24. Devereaux PJ, Yang H, Yusuf S, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet 2008;371:1839–47.
25. Defilippi CR, de Lemos JA, Tkaczuk AT, et al. Physical activity, change in biomarkers of myocardial stress and injury, and subsequent heart failure risk in older adults. J Am Coll Cardiol 2012;60:2539–47.
26. Rubin J, Matsushita K, Ballantyne CM, Hoogeveen R, Coresh J, Selvin E. Chronic hyperglycemia and subclinical myocardial injury. J Am Coll Cardiol 2012;59:484–9.

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